

Semipermanent and Permanent Injectable Fillers

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KEYWORDS

- Semipermanent and permanent fillers
- Hyaluronic acid • Calcium hyaluronic poly(lactic acid)
- Polymethyl methacrylate

Soft-tissue augmentation dates back more than 100 years ago, when autologous fat grafts were used to restore facial volume defects.¹ Paraffin was used for some time but fell out of favor because of a high incidence of foreign-body reactions. In the early 1950s, liquid silicone was first injected for soft-tissue augmentation. It was used widely until 1982, when the US Food and Drug Administration (FDA) temporarily banned its use over concerns of possible toxicity. Following the ban on liquid silicone, injectable bovine collagen became available in the United States in the 1980s and quickly became the gold standard of treatment to which many new dermal fillers are still compared. Although some may question the duration of effect of collagen, human collagen remains an agent of comparison in many pivotal trials.

Today, an impressive array of injectable dermal fillers for facial soft-tissue augmentation is available in the United States. These agents, most of which were introduced in the last half decade, represent a variety of semipermanent and permanent fillers across several categories. Physicians can choose between semipermanent fillers, such as hyaluronic acid derivatives (HA), calcium hydroxylapatite (CaHA), and poly-L-lactic acid (PLA), and longer-lasting, so-called “permanent fillers,” such as polymethyl methacrylate microspheres (PMMA), highly purified forms of liquid silicone, and hydrogel polymers.

While these fillers are generally safe, effectiveness is related to areas of injection and physician expertise. Each has its own specific properties and longevity that makes it more suitable for certain uses than for others. Semipermanent fillers must be

repeated at regular intervals, although with certain products the filler is replaced by the patients' own collagen over the course of several treatments. Permanent fillers require minimal touch-ups and have long-lasting effects of 5 years and longer.

SEMI-PERMANENT FILLERS

Calcium Hydroxylapatite

CaHA is a normal component of human bone and teeth and has been used as implant or coating material in dentistry and other therapeutic areas for more than 20 years. The filler is composed of CaHA microspheres (25–45 microns) suspended in an aqueous carboxymethylcellulose gel carrier. Radiesse (Bio-Form Medical, San Mateo, California) is the dermal filler containing CaHA. Skin testing is not required.

Mechanism of action

The mechanical filling and volume enhancement occurs following injection, when the gel carrier and CaHA microspheres displace surrounding soft tissue. As the gel is phagocytized, the process of neo-collagenesis begins in and around the microspheres, stimulating the gradual growth of the patients' own collagen (**Fig. 1**).² The spherical CaHA particles are gradually broken down and degraded by way of normal metabolic processes and eliminated as calcium and phosphate ions through the urinary system. The proliferation of collagen along with the slow breakdown of the CaHA is understood to account for the prolonged effects.³

Indications

CaHA is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles

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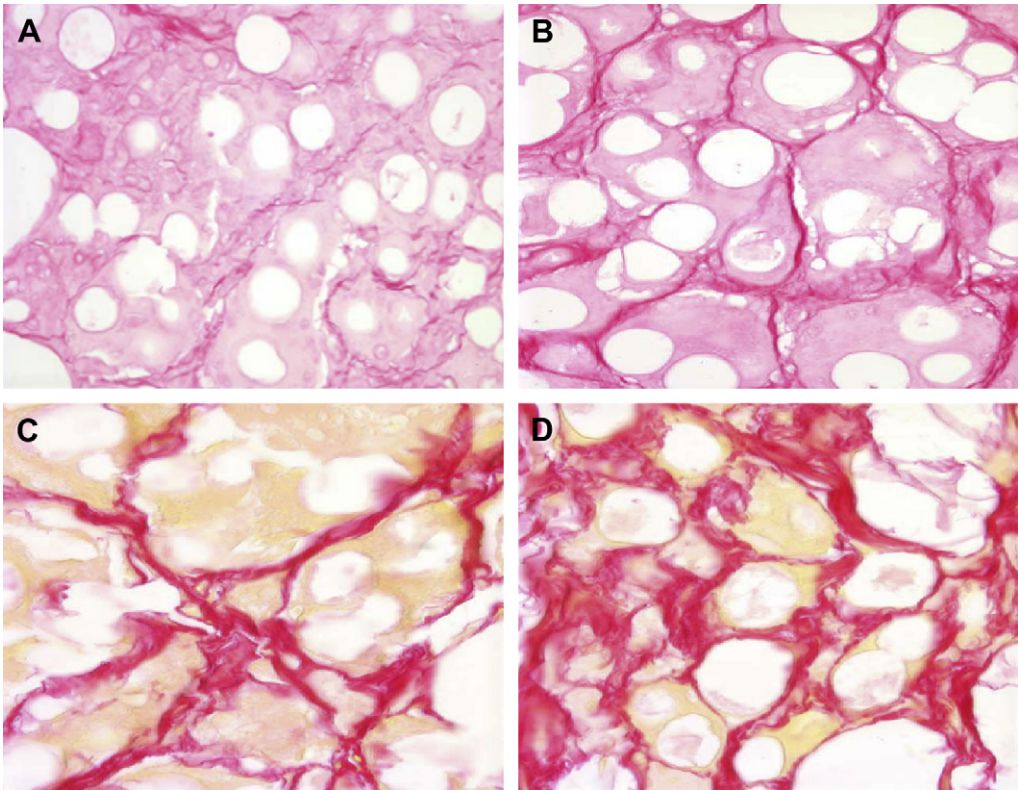


Fig. 1. (A–D) Histology studies demonstrate increased collagen deposition around CaHA microspheres over 4 to 78 weeks. Collagen fibers are represented by the darker areas. (From Coleman KM, Voights R, DeVore DP, et al. Neocollagenesis after injection of calcium hydroxylapatite composition in a canine model. *Dermatol Surg* 2008;34:553–5; with permission.)

and folds, including nasolabial folds (**Fig. 2**), and for the correction of HIV-associated facial lipoatrophy (**Fig. 3**). It is also indicated for vocal cord insufficiency, oral/maxillofacial defects, and radiographic tissue marking. Off-label facial uses also include correction of marionette lines and oral commissures, prejowl sulcus, cheek-volume loss, and dorsal nasal deformities. In its present formulation, CaHA is not appropriate for use in the lips.

Efficacy and safety

CaHA was compared with a human-collagen product in a United States pivotal trial of 117 subjects with moderate to severe nasolabial folds. These subjects were randomized to receive CaHA on one side of the face and an existing human collagen (HC) product (Cosmoplast, Inamed, Santa Barbara, California) on the other. CaHA provided significantly longer correction than HC,

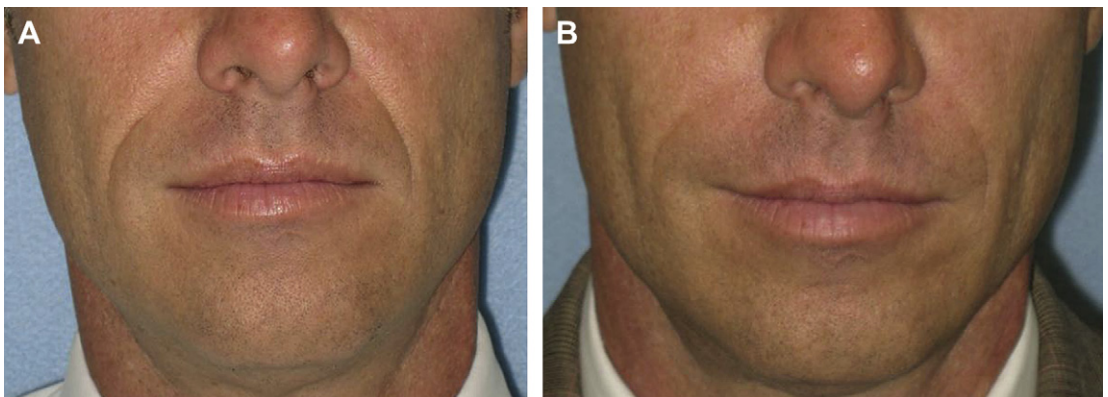


Fig. 2. (A, B) Pretreatment and posttreatment photographs of injection with Radiesse for nasolabial folds. Total volume injected into nasolabial folds was 1.3 mL. (Courtesy of D. Jones, MD, Los Angeles, CA.)

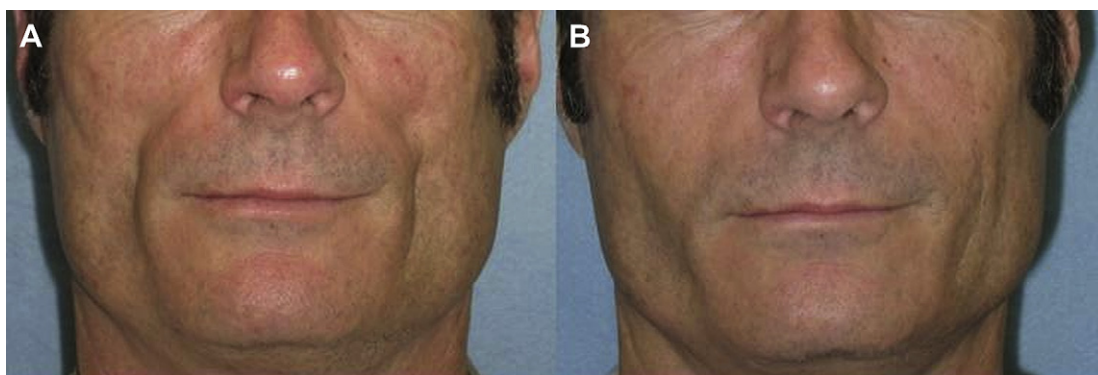


Fig. 3. (A, B) Pretreatment and posttreatment photographs of injection with Radiesse for HIV-associated facial lipatrophy. (Courtesy of D. Jones, MD, Los Angeles.)

and the favorable adverse event profile was similar to HC.⁴

In this split-face study, the mean change in pretreatment score using the Lemperle Rating Scale over 6 months was 1.23 for CaHA and 0.05 for HC. Dramatic differences between CaHA and HC were also noted in Global Aesthetic Improvement Scale (GAIS) ratings at 6 months. For CaHA, 94.6% of folds were graded improved, much improved, or very much improved, compared with 2.7% for HC. Data for up to 3 years has been gathered and is now in review by investigators. Early analysis suggests some residual effect in some patients for up to 36 months (Brian Pilcher, PhD, San Mateo, CA, personal communication, April 2009).

Adverse events were limited to erythema, edema, and ecchymoses. Edema and bruising were more common on the CaHA-treated sides than those treated with HC ($P < .0001$). Edema and bruising lasted approximately 1 week after any injection and the average duration for erythema was approximately 2 to 3 weeks, with no significant difference between the two materials. One nongranulomatous nodule was observed with CaHA compared with three with HC. All adverse events resolved without sequelae. In addition to the CaHA/HC study, another study found longer lasting results and increased satisfaction with CaHA when compared with two hyaluronic acid products.¹⁶

In a recent study, Busso and colleagues sought to determine whether the addition of anesthetic agents, such as lidocaine, to prefilled CaHA syringes might provide sufficient anesthetic prophylaxis to reduce the need for conventional anesthetic pretreatment procedures. The study demonstrated that the addition of lidocaine to CaHA syringes can be added safely without harmful changes in the physical properties of the original soft-tissue filler.⁵ Additional studies are underway to determine whether the addition of lidocaine

alters patients' discomfort, durability, and efficacy. It is the author's opinion that, as described in Busso's manuscript, addition of 0.15 cc 1% lidocaine with epinephrine to the 1.5 cc syringe and mixed by way of a female to female adaptor is revolutionary, dramatically lessens patients' discomfort, and is rapidly becoming the standard of care.

Clinicians have speculated whether CaHA posed any confounding radiographic properties. Caruthers and colleagues set out to answer this question and found that CaHA is not consistently evident on X ray but is clearly visible on CT. However, CaHA is unlikely to be confused with usual abnormal and normal radiographic findings. Although usually visible on CT, its appearance is distinct from surrounding bony structures, does not obscure underlying structures, and does not interfere with normal analysis.⁶ In summary, while visible on CT and X ray, CaHA does not interfere with usual interpretation of the radiographs, and therefore, does not pose overt radiographic safety concerns.

Technique

CaHA should be injected in small amounts in a retrograde fashion into the immediate subcutaneous plane or epiperiosteal plane, using a linear retrograde tunneling technique. Cross-hatched linear threading may also be employed. Overcorrection should be avoided. The nondominant index finger should be used to guide the needle and the thumb and forefinger used to mold the product and to remove any contour irregularities. CaHA should be injected very slowly in long, linear microthreads of approximately 0.05 mL per pass. Extreme caution should be taken when injecting into the subdermal plane around the superior nasolabial fold, where the angular artery and branches are present (Fig. 4). Occlusion of this vessel can occur by way of external compression from CaHA or by injection of CaHA directly into the lumen of the vessel, creating embolic ischemia

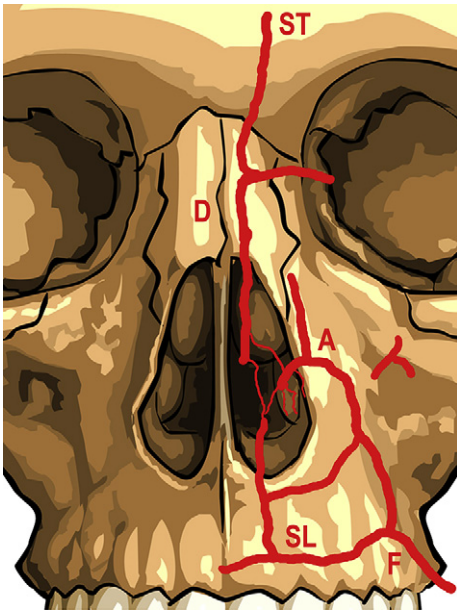


Fig. 4. Vascular anatomy of the midface. The angular artery (a branch of the facial artery) anastomoses with the supratrochlear and dorsal nasal arteries (branches of the ophthalmic artery), joining the external carotid artery network with the internal carotid artery network. Occlusion or embolic events involving this network can lead to extensive tissue necrosis. ST, supratrochlear artery; D, dorsal nasal artery; A, angular artery; SL, superior labial artery; F, facial artery.

and tissue necrosis of the nasal alar region along the distribution of the angular arteries or its branches. Reports of alar vascular necrosis have been reported to the author and the superior nasolabial fold should be considered a high-risk area not only for CaHA but for all injectable fillers.

It is particularly important to use sufficient volume of CaHA for the treatment of HIV-related lipoatrophy. While previous studies have demonstrated different efficacy endpoints, such as photographic documentation of global improvement and change in mean skin thickness using ultrasound or skin calipers, treatment often falls short of optimal correction in clinical practice. In a recent study by Carruthers and Carruthers, the authors defined optimal correction as “very much improved” on the GAIS scale, where a touch up is not required, and sought to determine the volume necessary to achieve optimal correction. Using a mean cumulative volume of 13.4 mL of CaHA, subjects in the Carruthers’ study achieved the top GAIS score of “very much improved” in 80% of subjects at 3 months and 59% at 6 months, compared with 26% at 3 months and 7% at 6 months in a similar study by Silvers that used a mean cumulative volume of 8.4 mL of CaHA.^{7,8}

Poly-L-lactic Acid

PLA is a synthetic polymer that is biodegradable and resorbable. Injectable PLA (Sculptra, Dermik Laboratories, Berwyn, Pennsylvania) consists of microparticles of PLA in a sodium carboxymethyl-cellulose gel. The filler must be reconstituted with sterile water before administration. No skin test is required. PLA was approved by the FDA in 2004 for the treatment of HIV-related facial lipoatrophy, although the product is used off label for limited age-related lipoatrophy in patients who do not have HIV.

Mechanism of action

PLA is administered into the subcutaneous plane. There, the suspension of reconstituted PLA provides mechanical correction and filling. Immediate volumizing is mostly from fluid that becomes absorbed over a few days. Over weeks to months, the PLA microparticles are gradually degraded, while treated areas undergo subtle volume expansion as the host tissue responds to the PLA.⁹ The microparticles of PLA become surrounded in a capsule of connective tissue consisting of connective tissue cells and inflammatory cells, such as macrophages, lymphocytes, mast cells, and foreign body giant cells. As time passes, there is a fibrous-tissue response with collagen deposited around the foreign body reaction. This fibrous response is thought to provide sustained correction.

Indications

PLA is indicated specifically for the correction of HIV-related facial lipoatrophy. It is also approved for correction of nasolabial folds in HIV negative patients. The filler works best for volume correction, not specific depressions. PLA is also used off label in non-HIV-infected patients who have panfacial stage 1 facial lipoatrophy, a condition that is often a consequence of aging in healthy, lean individuals. Monthly injections of one to two vials into the subcutis over many treatments (4–6 is usual) often achieve restoration of subcutaneous volume (**Fig. 5**). Correction of subcutaneous fat loss will often last for 12 to 24 months. After this time, patients will often seek reinjection. In the author’s experience, PLA is often not successful in treating more advanced cases of HIV facial lipoatrophy.

Efficacy and safety

PLA was first approved in 2004 using a fast-track process, an accelerated review procedure often used for HIV drugs. Efficacy and safety data for the approval was based on data from physician-sponsored Investigational Device Exemption studies in the United States and the European VEGA study. The VEGA study followed 50 subjects

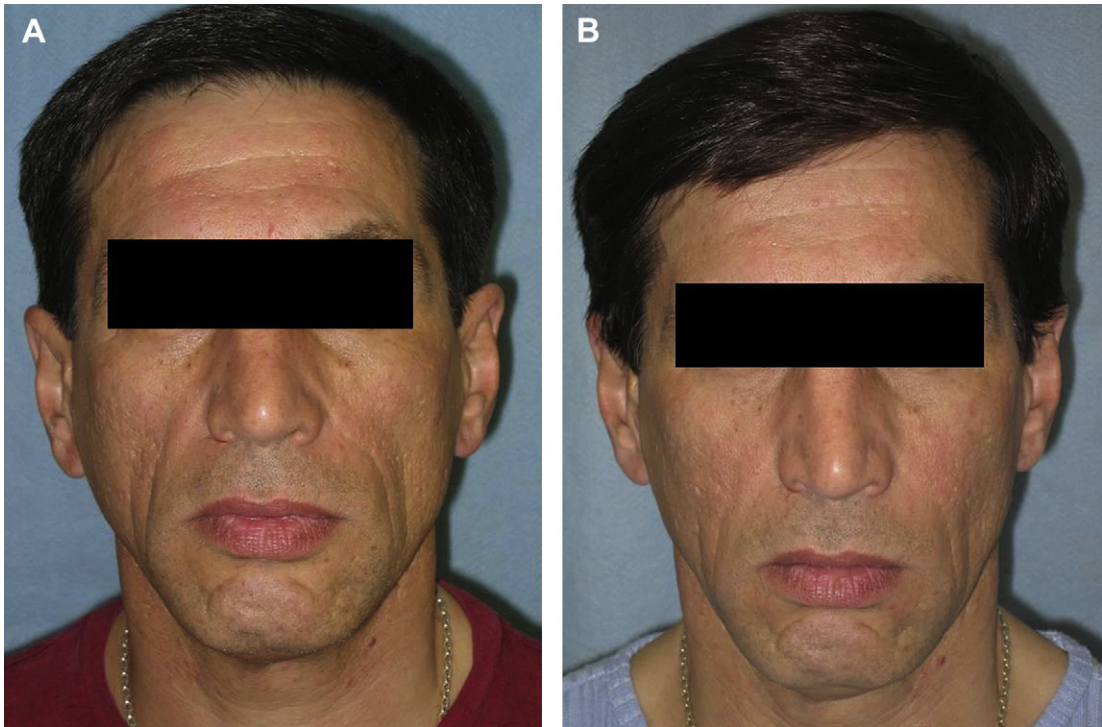


Fig. 5. (A) Pretreatment of age-related, non-HIV facial lipoatrophy compared with 1 month following the final treatment with eight vials of Sculptra injected in four treatment sessions over 3 months. (B) One month after last injection. (From Jones D, Vleggaar D. Technique for injecting poly-L lactic acid. *J Drugs Dermatol* 2007;6:S13-7; with permission.)

treated with PLA for 96 weeks.¹⁰ Subjects with HIV-associated facial lipoatrophy received four sets of injections: Day 0, followed by every 2 weeks for 6 weeks. Subjects were evaluated using clinical examination, facial ultrasonography, and photography. At entry, the median facial fat thickness was 0 mm. The median total cutaneous thickness increased significantly from baseline (up to 7.2 mm at weeks 48 and 72). By week 96 the median total thickness was 6.8 mm. No significant adverse events were observed. In 22 (44%) subjects, palpable but nonvisible subcutaneous nodules were observed, which tended to spontaneously resolve with time. The study did not use ratings of pre- and posttreatment photographs by experienced physicians not performing the treatment to measure whether optimal correction with complete restoration of cheek contours was achieved. Approval for aesthetic use was gained in mid 2009 based on the results of a randomized, evaluator-blinded, parallel-group, multicenter study of 233 patients carried out in immune competent patients. The treatment phase consisted of 1 to 4 visits at 3-week intervals during which patients received bilateral injections (average of all injections was 2.3 vials) of Sculptra®Aesthetic¹¹ (n = 116) or collagen (n = 117)

into the left and right nasolabial fold wrinkles. The follow-up phase consisted of visits at week 3 and months 3, 6, 9, and 13 after the last treatment. Of the 116 patients treated with Sculptra®Aesthetic, 106 patients completed the study and continued into the long-term surveillance phase, which extended to 25 months. Ninety-five patients completed the surveillance phase. Evaluation was done through use of the Wrinkle Assessment Score (WAS) coding system, (0 = no wrinkles; 5 = a very deep wrinkle or redundant fold). Improvements from baseline at 25 months proved to be consistent, progressive, and statistically significant at each time point measured ($P < 0.001$) 100% of patients improved at week 3; 88.7% at month 13; and 86.3% at month 25.

Patients consistently reported high satisfaction with their Sculptra®Aesthetic treatment results with 80% of patients satisfied with results at 25 months. In physician-reported adverse events with Sculptra®Aesthetic: 8.6% of patients experienced papules and nodules up to 13 months falling to 1–1.9% at 25 months.

An increased risk of papules and nodules in the periorbital area has been reported in published literature therefore use in the periorbital area is not recommended. Use of Sculptra®Aesthetic is

contraindicated in the lips, in individuals with known hypersensitivity to any of its components, or in patients with known history of or susceptibility to keloid formation or hypertrophic scarring. Sculptra®Aesthetic should not be injected in areas with active skin infection or inflammation.

In addition to the adverse events in these studies, persistent granulomatous reactions have been observed (Fig. 6).¹²

Technique

PLA should be injected into the subdermal plane, not into the dermis, to limit the likelihood of nodule and papule development. Red, palpable, persistent dermal nodules may occur with intradermal injection. Dermal defects are better treated with an HA or collagen filler. A linear retrograde technique, with a cross-hatching approach, should be used with a 25-gauge, 1-in or 2-in needle. Smaller bore needles tend to become easily clogged. Practitioners should use 1 mL tuberculin syringes, and shake the solution well before transferring to syringe and immediately before injection.

The 25-gauge needle entry site may be anesthetized with small, intradermal injections of 1% lidocaine with epinephrine through a 30-gauge needle, resulting in tolerable injections. Intravascular injection should be avoided; the angular artery runs in the immediate subdermal plane in the area of the superior nasolabial fold. Injection of the parotid duct, which overlies the buccinator muscle in the lateral cheek, should also be avoided.

It is often helpful to outline the treatment area before injection. The treated area must not extend above the inferior orbital rim. To prevent contour irregularity and visible or palpable nodules in the infraorbital area, the product must be injected

epiosteally in small amounts, deep to the muscle layer, using a serial puncture technique. Patients should also be made aware that the immediate posttreatment appearance will fade within 2 to 4 days. This instantaneous effect is caused by fluid from the filler, which causes edema upon injection. Optimal augmentation will become apparent after multiple treatments at 3- to 4-week intervals, as new collagen is regenerated.¹³

Although the package insert recommends reconstitution of each vial of PLA with 3 mL of sterile water, subcutaneous lumps also can be avoided if each vial is reconstituted with 5 mL of sterile water, or 4 mL of sterile water and 1 mL of 1% lidocaine without epinephrine, at least 24 hours before injection. The reconstituted vial should be vigorously shaken immediately before transfer into the syringe as settling of the product in the syringe may lead to uneven application and contribute to nodule formation.¹³ Unlike CaHA, which generally is not massaged by patients, those who have PLA injections should be instructed to frequently massage the treated area in the days to weeks following the procedure to prevent the formation of uneven or lumpy fibroplasia. Some advocate the “rule of 5s” whereby the patient massages the area for 5 minutes, 5 times daily, for 5 days after the injection.

PLA effect is subtle, and many treatments may be required to reach optimal correction. Duration is generally 1 to 2 years.

Hyaluronic Acid Derivatives

Hyaluronic acid, an important natural component of human skin, is a glycosaminoglycan

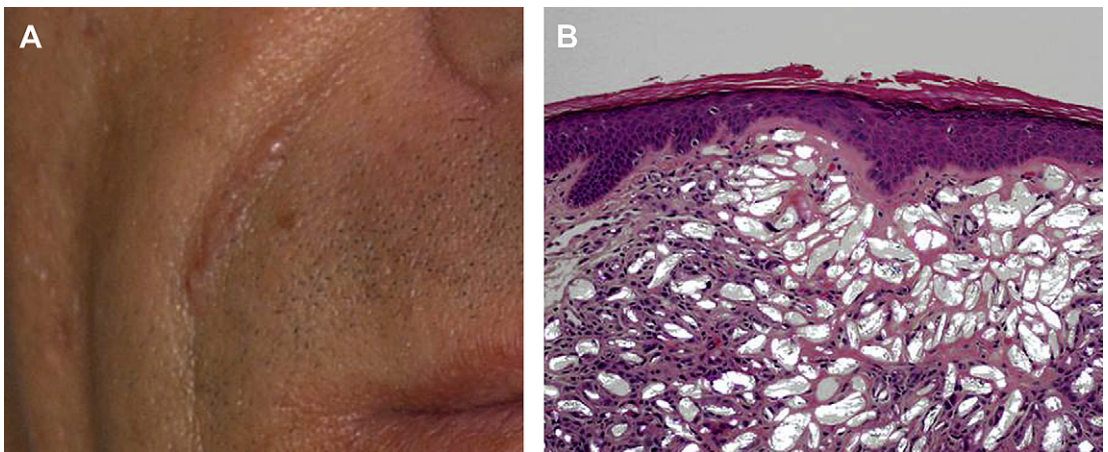


Fig. 6. (A, B) Persistent granulomatous reaction to PLA. (From Wildemore JK, Jones DH. Persistent granulomatous inflammatory response induced by injectable poly-L-lactic acid for HIV lipoatrophy. *Dermatol Surg* 2006;32:1407–9; with permission.)

polysaccharide comprised of residues of the monosaccharides *D*-glucuronic acid and *N*-acetyl-*D*-glucosamine. HA fillers comprise the major share of the United States market place for injectable fillers, with Juvederm (Allergan, Irvine, California) and Restylane (Medicis, Scottsdale, Arizona) dominating the market.

Most hyaluronic acid derivatives are superior to bovine collagen 6 months after injection. For example, in the pivotal study comparing three formulations of Juvederm with Zyplast, 81% to 90% of nasolabial folds treated with Juvederm maintained a clinically significant improvement from baseline for at least 6 months, compared with 36% to 45% with bovine collagen.¹⁴ The pivotal trial for Restylane evaluated 138 subjects who received Restylane in one nasolabial fold and Zyplast in the contralateral fold. Using the GAIS, investigators rated 62% of folds superior with Restylane at 6 months compared with Zyplast, and 8% rated Zyplast superior to Restylane.¹⁵

Generally, hyaluronic acid-derivative-associated correction has a cosmetic effect for approximately twice as long as bovine collagen (ie, persistence for 4–6 months rather than 2–3 months).⁶ However, recent studies of nonanimal HA derivatives have demonstrated long-lasting effectiveness of up to 18 months after retreatment with either Juvederm or Restylane because of the apparent development of fibroplasia around the injected product. Therefore, certain hyaluronic acids should be considered semipermanent fillers.^{16,17}

Serious adverse events are rare. In a retrospective analysis of the safety of nonanimal, stabilized

HA, major adverse events included hypersensitivity reactions, localized granulomatous reactions, bacterial infection, and acneiform and cystic lesions.¹⁸ One salient advantage of hyaluronic acid is that adverse reactions or unwanted placement of product may be quickly and safely reversed with hyaluronidase.¹⁹ Other HA currently FDA-approved include Prevelle Silk (Mentor, Irving, Texas), a 5.5 mg/cc HA with pre-incorporated lidocaine. Compared with Juvederm and Restylane, Prevelle Silk is a less concentrated or lighter HA with less lift capacity and a shorter tissue residence time. Also FDA-approved is Eleveess (Anika, Woburn, Massachusetts), which is a higher concentration 28 mg/cc HA (Table 1). Several other HA are being investigated in clinical trials in the United States. They include Puragen Plus (Mentor Corporation, Santa Barbara, California), which contains lidocaine integrated directly into the formula; Belotero Soft and Belotero Basic (An-teis, Geneva, Switzerland), and Teosyal (Teoxane Laboratories, Geneva, Switzerland).

PERMANENT FILLERS

Liquid Silicone

Liquid silicone (LIS) was first used as an injectable filler in the 1950s. Before collagen injectable fillers became available in the early 1980s, LIS was the injectable filler of choice. There was no standardized FDA-approved product and many products of varying purity were injected often in large bolus form, which led to frequent product migration and foreign-body reactions. Subsequently, in the early 1990s, all forms of silicone for cosmetic implantation were banned by the FDA because of possible

Table 1

Currently available dermal fillers approved by the US Food and Drug Administration (May, 2009)

Temporary fillers

Bovine collagen	Zyplast, Zyderm (Allergan, Irvine, CA)
Human collagen	Cosmoderm, Cosmoplast (Allergan, Irvine, CA)
Porcine collagen	Evolence (Colbar, Herzliya Israel)
Hyaluronic acid	Prevelle Silk (Mentor, Irving, TX), Eleveess (Anika, Woburn, MA)

Semipermanent fillers

Calcium hydroxylapatite	Radiesse (BioForm, San Mateo, CA)
Poly-L-lactic acid	Sculptra (Dermik, Berwyn, PA)
Hyaluronic acid	Restylane, Perlane (Medicis, Scottsdale, AZ); Juvederm (Allergan, Irvine, CA)

Permanent fillers

Liquid silicone	Silikon-1000 (Alcon, Fort Worth, TX); Adatosil-5000 (Escalon Ophthalmics, Skillman, NJ)
Polymethyl methacrylate	Artefill (Artes, San Diego, CA)

toxicity and systemic reactions related to LIS and silicone breast implants.

After the FDA resolved safety issues regarding silicone breast implants and LIS, in the late 1990s, two new forms of highly purified liquid silicone were approved (Silikon-1000 and Adatosil-5000) for use as an intraocular implant to treat retinal detachment. While this use is the only official indication for LIS, the FDA Modernization Act of 1997 makes off-label uses legal, provided that the physician or drug manufacturer does not advertise for such use. LIS is now used off label for soft-tissue augmentation (see indications discussed later). Silikon-1000 has a lower viscosity and is the most suitable for injectable soft-tissue augmentation, as it is easier to inject through smaller gauge needles.

Current opinion on liquid injectable silicone is polarized between opponents and advocates. Opponents argue that despite use of proper technique and products, serious adverse events are common and unpredictable. Proponents rely on a wealth of anecdotal data to argue that liquid injectable silicone is safe and effective as long as three rules are employed: (1) use highly purified FDA-approved LIS; (2) employ microdroplet serial puncture technique (defined as 0.01 cc per injection site injected into the subdermal plane); and (3) use small volumes (0.5 mL for smaller defects and up to 2 mL for larger areas of atrophy) at each session with multiple sessions staged at monthly intervals or longer.

Mechanism of action

After LIS is injected, a capsule of new collagen develops to encircle each microdroplet of silicone. This process continues for about 3 months, during which time the collagen capsule adds volume to the augmentation of the LIS microdroplet. The collagen also holds the droplets in place to prevent migration.⁹

Indications

Although LIS is used off label for many indications, it is the author's opinion that LIS should not be routinely employed for the average cosmetic patient until longer-term studies with current products resolve some of the controversy regarding longer-term safety and efficacy. However, for the unique and disfiguring defects associated with HIV facial lipoatrophy and serious acne scarring, LIS produces cosmetically superior and more durable results than currently available less-permanent options (See Efficacy and safety discussed later).

Efficacy and safety

LIS is an excellent choice for HIV-associated facial lipoatrophy. In one trial, highly purified 1000-cSt silicone oil was studied among 77 subjects to determine the number of treatments, amount of silicone, and time required to reach complete correction. Subjects received 2 mL of Silikon 1000 at monthly intervals with the microdroplet technique until optimal correction was achieved. The researchers elucidated two important findings: (1) all three of these parameters were directly related to the initial severity of lipoatrophy, and (2) highly purified 1000-cSt silicon oil is a safe and effective treatment option for HIV-associated lipoatrophy (Fig. 7).²⁰ Five-year data is now available on this cohort and no serious adverse events have been found (D. Jones, unpublished data).

Using the microdroplet, multiple-injection technique, Barnett and Barnett have had success with injections of LIS for acne scars lasting over a 10-, 15-, and 30-year follow-up periods.²¹

Technique

Clinicians should inject only highly purified FDA-approved LIS, such as Silikon-1000, using the microdroplet serial puncture technique (0.01 mL or less injected through a 27-gauge needle into the immediate subdermal plane at 2 mm to 4 mm intervals). Intradermal injections should be avoided, as these may create intradermal papules.²² However, intradermal injections may be used for atrophic dermal acne scars, using 0.001 mL microdroplets.

Very small amounts of LIS should be injected at monthly intervals, or longer. The immediate goal is undercorrection. Optimal correction occurs slowly as fibroplasia develops around the microdroplets, creating further tissue augmentation and anchoring each microdroplet into place.

Polymethyl Methacrylate

Injectable PMMA (ArteFill, Artes Medical, San Diego, California) is a suspension of 20% PMMA smooth microspheres and 80% bovine collagen. ArteFill is the product of third-generation PMMA microsphere technology. Previous generations include Arteplast (used in Germany from 1989 to 1994) and Artecoll (used worldwide, except in the United States and Japan, from 1994 to 2006). Artefill represents a third-generation product containing fewer nanoparticles (less than 20 microns), which were thought to be associated with granulomatous reactions observed with previous generations. ArteFill was approved by the FDA in 2006 for the correction of nasolabial folds. However, Artes filed for Chapter 7 bankruptcy in December 2008, and was acquired by

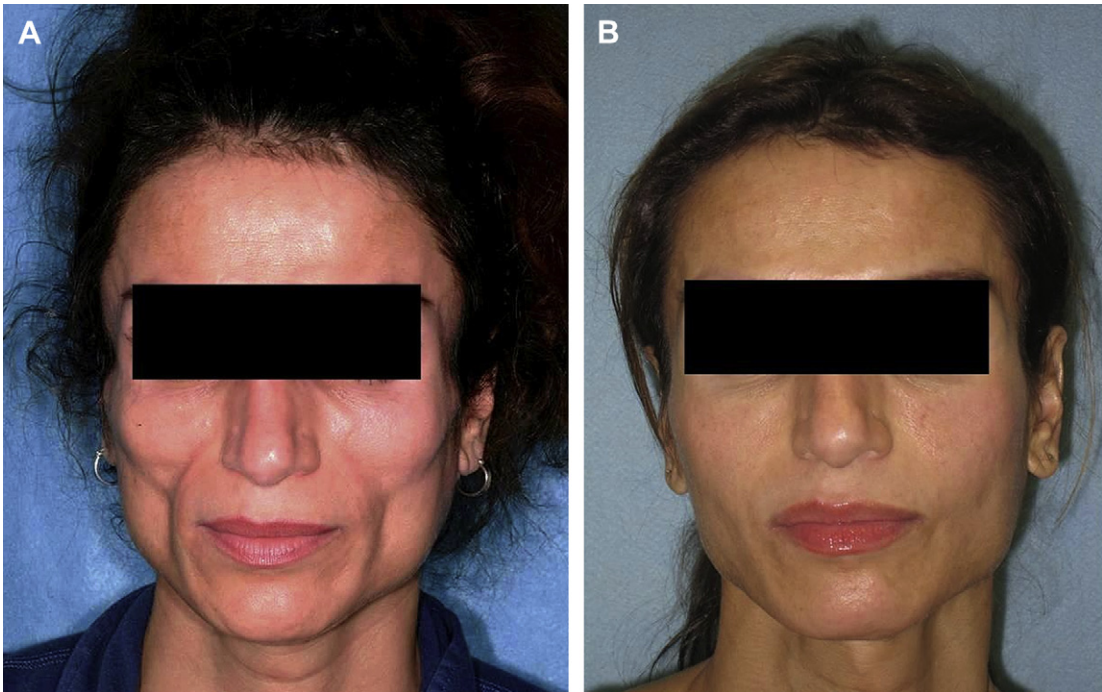


Fig. 7. (A, B) Pretreatment and posttreatment liquid injectable silicone for HIV-associated facial lipoatrophy. (Courtesy of D. Jones, MD, Los Angeles, CA.)

Suneva (San Diego, California) which now owns and distributes ArteFill.

Mechanism of action

After PMMA is injected, the collagen vehicle is absorbed within 1 to 3 months. Afterward, new collagen is deposited by the host to encapsulate and engulf the remaining estimated 6 million PMMA particles in 1 mL of ArteFill. This process contributes to tissue augmentation through fibroplasia. Although collagen is absorbed, the PMMA is permanent and not reabsorbed.⁹

Indications

Injectable PMMA is indicated for nasolabial folds. It is also used off label for glabellar frown lines, radial lip lines, and mouth corners.

Injectable PMMA is contraindicated for use in patients who have a positive result to the required ArteFill skin test; patients who have severe allergies (as indicated by a history of anaphylaxis or multiple severe allergies); patients who have known lidocaine hypersensitivity; patients who have a history of allergies to bovine collagen products; and patients who have known susceptibility to keloid or hypertrophic scarring. The product should not be used for lip augmentation.

Efficacy and safety

The United States pivotal clinical trial for ArteFill was a controlled, randomized, prospective,

double-masked trial of 251 subjects at eight centers across the United States. Subjects received either ArteFill or bovine collagen dermal filler (control). Efficacy was rated by masked observers using a photographic Facial Fold Assessment Scale. The study demonstrated a significant improvement with ArteFill compared with the control group at 6 months ($P < .001$) in nasolabial folds. A subset of subjects was observed at 12 months and all showed persistent wrinkle correction (**Fig. 8**).²³

A subgroup of 69 subjects returned for follow-up 4 to 5 years later. Investigator Facial Fold Assessment ratings at 4 or 5 years were improved from baseline by 1.67 points ($P < .001$). Nearly all subjects (95.5%) reported that they were at least somewhat satisfied and 81.8% reported that they were either satisfied or very satisfied.²³

Five subjects reported six late, adverse events that occurred from 2 to 5 years after the initial injection. Of these, four were mild cases of lumpiness, and two were severe. The total number of late, adverse events was 6 of 272 (2.2%) of wrinkles injected.²⁴

Granulomatous reactions (manifested by inflamed red nodules) may be treated with intralesional cortisone combined with antibiotic therapy.

Technique

Injectable PMMA is placed into the dermal-subcutaneous junction using the tunneling or linear

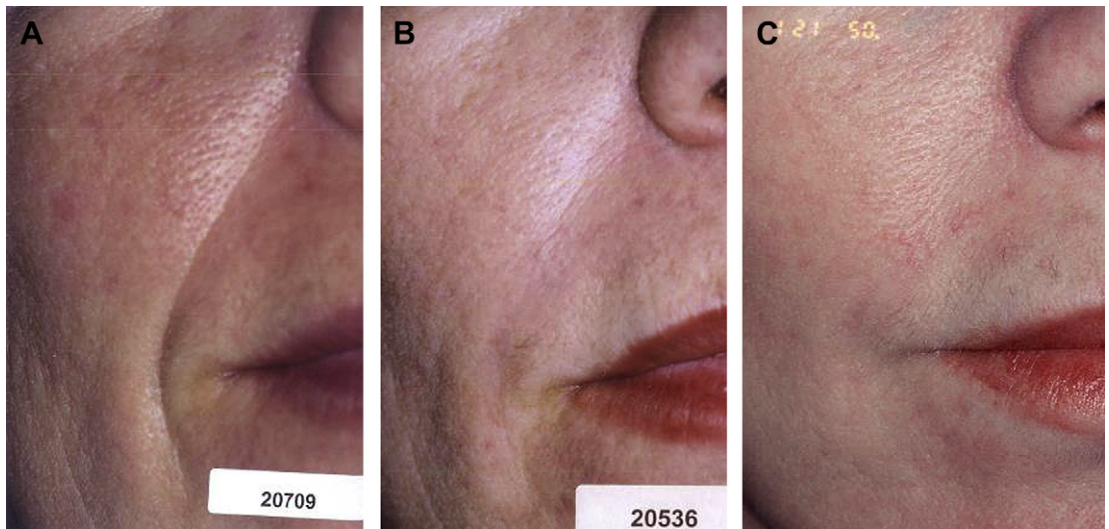


Fig. 8. Results of ArteFill for the treatment of nasolabial folds at pretreatment, 1 year posttreatment, and beyond 1 year posttreatment. (A) Pretreatment. (B) 1 year posttreatment. (C) Greater than 1 year posttreatment. (From Cohen SR, Holmes RE. Artecoll: a long-lasting injectable wrinkle filler material: report of a controlled, randomized, multicenter clinical trial of 251 subjects. *Plast Reconstr Surg* 2004;114:964–76; with permission.)

threading technique with a 26-gauge, 5/8-in needle. Overcorrection is not recommended. It is preferable to inject more deeply than superficially, as the risk of wasted material is less problematic than superficial injection, which can cause permanent skin surface texture or color impairment.

Patients should be evaluated 4 to 6 weeks after the injection to assess the need for further treatments. Optimal correction usually requires two to three treatments, and touch-up implantations should be at intervals of at least 2 weeks or longer depending upon the amount of implant used, the site of placement, and the dynamics of the corrected sites.

Investigational Permanent Agents

Hydrogel polymers

Hydrogel polymers are a novel class of fillers, comprised mostly of water with a small amount of synthetic polymer. The so-called injectable “endo-prosthesis” agents include Bio-Alcamid (Polmekon, Milan, Italy) and Aquamid (Aquamid, Ferrosan, Copenhagen, Denmark), both of which are used in Europe but are not yet FDA approved. These nonbiodegradable fillers are composed of 96% water and 4% synthetic polymer (polyalkylimide, in the case of Bio-Alcamid, and polyacrylamide for Aquamid). Both agents are used for large-volume augmentation, such as hemifacial lipoatrophy (Romberg’s disease) or HIV-associated lipoatrophy.

Mechanism of action

Once injected, the gel particles become covered by a thin collagen capsule (0.02 mm) which completely

surrounds the particles and isolates them from the host tissues, creating an injectable prosthesis. According to the manufacturer, Bio-Alcamid has much stability, integration among living tissues, and more simple removal, if required, than other dermal fillers. The results are considered permanent, but removal can be done through aspiration. Full efficacy of removal through aspiration remains unclear.

Indications

While both agents are used for replacement of facial volume caused by lipoatrophy, they are also used for the treatment of nasolabial folds, lip augmentation, depressed scars, and enhancement of cheekbones and jawline. They are not indicated for the treatment of fine wrinkles.

Efficacy and safety

Recent reports in the literature document the success of Bio-Alcamid for the treatment of HIV-associated facial lipoatrophy.^{25,26} According to the manufacturer, risk of infection or allergy is very low (0.6%) and only 0.2% of patients have had an immune response to the implant, which created localized swelling that required drainage over a 1- to 6-month period.

Late-appearing streptococcal bacterial abscesses have been reported. A paper by the author and colleagues follows five patients who received Bio-Alcamid for HIV-associated lipoatrophy and developed late-appearing streptococcal bacterial abscesses (Fig. 9).²⁷ In each case, an acute abscess developed several months and up to years after the initial injection of Bio-Alcamid. All

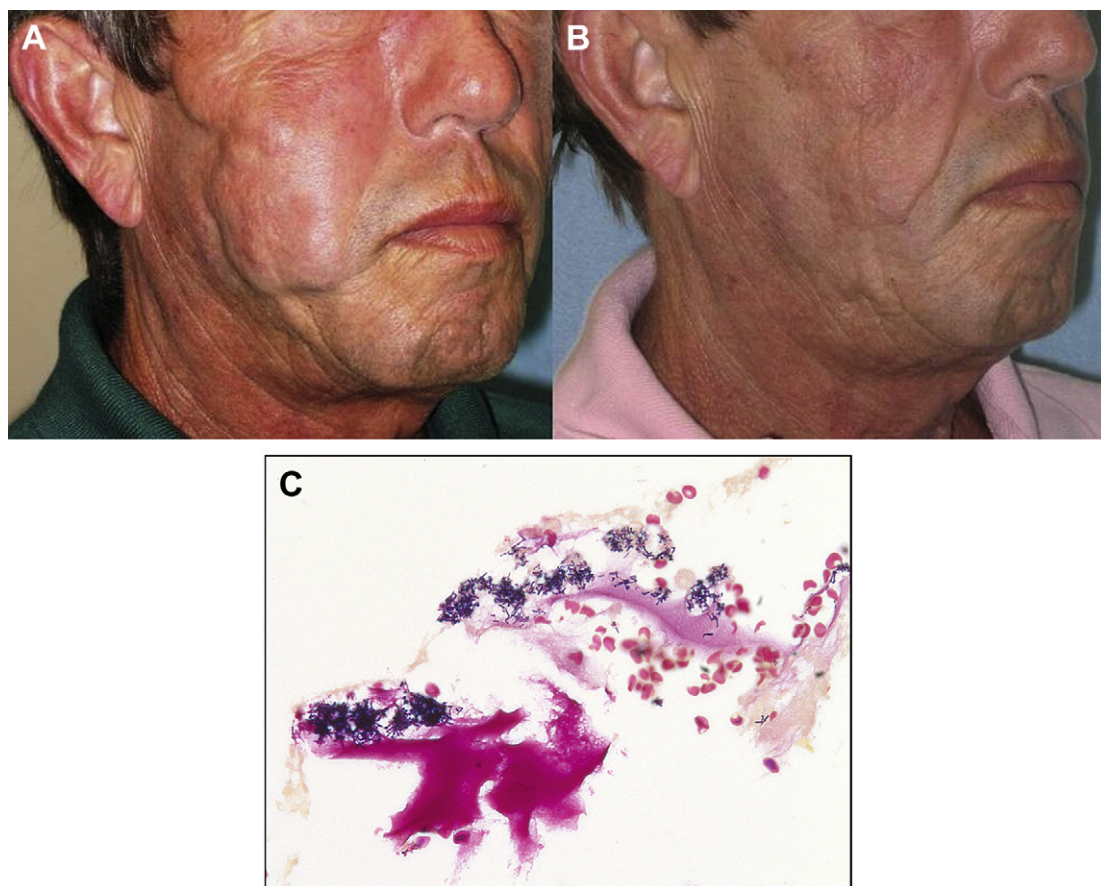


Fig. 9. Bio-Alcamid abscess preincision (A) and (B) postincision and drainage; gram stain of drained material reveals streptococcal bacteria (C). (Adapted from Jones DH, Carruthers A, Fitzgerald R, et al. Late-appearing abscesses after injections of nonabsorbable hydrogel polymer for HIV-associated facial lipoatrophy. *Dermatol Surg* 2007;33:S193–8; with permission.)

five cases responded quickly to drainage and antibiotic therapy, although in two cases the abscesses became recurrent. In one case the patient also developed methicillin-resistant *S. aureus* and required extensive intravenous antibiotic therapy.

Based on the cases, it appears that local oral streptococcal bacteria may be capable of directly invading implant material. It also seems possible that the bacteria may reach the implant through a needle puncture during a dental or surgical procedure, possibly warranting prophylactic antibiotic therapy before dental and surgical procedures in patients who have received Bio-Alcamid.

Bio-Alcamid and other hydrogel polymers carry the risk of foreign-body reaction, infection, migration, or granuloma formation.

Technique

These agents are injected subcutaneously, usually under local anesthesia, and massaged smooth by the clinician. A thin layer of collagen gradually forms around the injected gel over a period of 4

to 8 weeks when the gel becomes completely surrounded and isolated from host tissues, in effect making it an endogenous prosthesis.

SUMMARY

The use of dermal fillers has advanced significantly from its beginnings with fat grafts in the early 20th century to the full array of semipermanent and permanent fillers now available. Today's fillers are suitable for many indications and each has its own advantages and disadvantages.

Many novel dermal fillers that are already available in Europe are now undergoing FDA testing, and some of these will likely be approved for use in the United States within the next few years. They include the aforementioned investigational HA in the semipermanent class of fillers and hydrogel polymers among the permanent fillers. These fillers will expand the choices available to patients and physicians and promise to increase longevity and minimize adverse events.

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